B3

34. (Amended) Preparation as claimed in claim 31, wherein the concentration of said surfactant is between 20 and 50 mol-% of the concentration of said surfactant which would be required for causing said lipid to be solubilized, and the edge tension of said transfersomes is about 10 Piconewton or less.

B4

48. (Amended) Method as claimed in claim 46, further comprising determining the stability and the permeation capacity of said transfersomes by means of gravity or pressure filtration, through a fine pore filter.

B5

50. (Amended) Method as claimed in claim 46 wherein the content of said surface active substance is between 20 and 50 mol-% of the concentration of such substance which would be required for causing said lipid to be solubilized.

REMARKS

Claims 31-69 are currently pending in this application. In the Office Action dated December 4, 2000, the Examiner rejected claims 31-69 under 35 U.S.C. § 112, second paragraph as being indefinite; claims 31-42, 46-50, 52-60 and 63-69 under 35 U.S.C. § 102(b) as being anticipated by EP 0 220 797; claims 31, 32, 34-42, 46-47, 62-86 and 101-155 under 35 U.S.C. § 102(b) as being anticipated by Mayer; claims 31-69 under 35 U.S.C. § 103(a) as being unpatentable over EP 0 220 797 and claim 48 was rejected under 35 U.S.C. §103(a) as being unpatentable over EP 0 220 797, further in view of Mayer.

In view of the amendments made and arguments presented herein, the Applicant respectfully requests reconsideration of this application.

Objection to the Specification

In the Office Action, the Examiner objected to the disclosure because the specification does not contain a brief description of the drawings.

In response, the specification has been amended to include the following section titles: A background of the invention, a summary of the invention, a brief description of the drawings, a detailed description of the invention, and a detailed description of the preferred embodiments.

In view of the amendments made to the specification, Applicant respectfully requests that the Examiner withdraw the objection to the disclosure.

Rejections Under 35 U.S.C. § 112

In the Office Action dated December 4, 2000, the Examiner rejected claims 31-69 under 35 U.S.C. § 112, second paragraph as being indefinite.

The Examiner stated "claim 31 recites the percentages on weight basis and the dependent claim 34 recites mole percent. This is confusing."

In response, Applicant states that claim 31 recites the weight percent of the lipid content of the transfersome. Claim 34 recites the mol-% of the surfactant content of the transfersome. Applicant states that both weight percentage and molar percentage are well-known measurements to those of ordinary skill in the art. Therefore, it is respectfully submitted that one skilled in the art would not be confused by the use of these two different measurements of weight percentages, especially since the two different weight measurements are being used to describe two different ingredient contents.

The Examiner also stated that the statement "wherein the concentration of surfactants is between 20-50 mol-% of the concentration of said surfactant causes. . ." in claims 34 and 50 is confusing. Furthermore, the Examiner stated that "according to this claim the surfactant solubilizes the lipid and therefore, one would expect a solution and not transfersomes."

In response, Applicant points out that claims 34 and 50 have been amended to recite that the concentration of said surfactant "is between 20 and 50 mol-% of the concentration of said surfactant which would be required for the lipid to be solubilized. . . ." Applicant believes that this slight language change makes clearer that the lipid is not fully solubilized by the surfactant, unless the concentration of the surfactant is 100 mol-%. The mol-% of the surfactant as claimed in the present invention dose not reach 100 mol %, but rather it reaches between 20 and 50 mol-%, which provides for a more deformable carrier (e.g., transfersome) thus allowing the transfersome to reach its permeation capacity without causing a total solubilization of the lipid.

In addition, in rejecting claim 49 under §112, the Examiner asked "what is being conveyed through 'permeation capacity ----mechanical fragmentation' as recited in claim 49? How can fragmentation determine permeation capacity?"

In response, Applicant notes that aggregate capability to cross pores smaller than average aggregate size is due to non-destructive aggregate deformation, as specified in claim 31 and explained in the introductory section of the specification. If an aggregate is fragmented (to a size smaller than a pore diameter) prior to or during the passage through a pore, then the original barrier ceases to be an obstacle. In other words, transfersomes must be sufficiently stable to mediate significant transport across a semi-permeable barrier. The requirement for general stability notwithstanding, transfersome membranes must be able to become locally destabilized, and thus to gain flexibility over a limited part of surface area, to deform strongly. This is a key requirement for attaining the very high deformability of such aggregates.

Owing to the local membrane destabilization and deformability, transfersomes are better suited for adopting the form of a small vesicle under isotropic stress than are conventional liposomes, with at least ten times more rigid membranes. Note that when exposed to anisotropic stress, a stress such that induces longitudinal vesicle deformation, transfersomes are less prone to fragment than liposomes. It is therefore possible to gauge whether a given mixed lipid aggregate is rather close to transfersomes or liposomes, with regard to its mechanical properties, by studying the mechanically induced fragmentation of test aggregates under different conditions, e.g., by comparing the consequences of spatially uniform stress of an ultrasound device or a homogenizer vs. the results of directed stress caused by quasi-laminar flow through a pore. If a suitably chosen reference suspension, e.g., liposome or transfersome, is used together with test suspension, comparative experiments done with a single measuring device are sufficient (see FIG. 16).

Therefore, in view of the arguments presented above, Applicant respectfully requests that the Examiner's rejection of claims 31-69 under 35 U.S.C. § 112, second paragraph as being indefinite be withdrawn.

Finally, in the Office Action, the Examiner asked "what is being conveyed by 'phosphate salts thereof and sulfate salts thereof' as recited in claim 67?... Some of the compounds recited are salts of acids... For example, deoxycholate, myristate, oleate, etc., are anionic in nature having a metal cation... How can one form a further salt?"

In response, Applicant respectfully submits that often times it will not be possible to form different salts, but one can not completely rule out this possibility. In certain situations the affinity of a given substance for a new ion may be higher than for the original ion, therefore, leading to the formation of a different salt. Therefore, it is respectfully requested that the Examiner withdraw the rejection to claim 67.

Rejections Under 35 U.S.C. § 102

In the Office Action, the Examiner rejected claims 31-42, 46-50, 52-60 and 63-69 under 35 U.S.C. § 102(b) as being anticipated by EP 0 220 797. The Examiner stated that "EP discloses liposomes containing a drug, an amphiphilic liquid and a surfactant in instant amounts and a method of preparation (note the abstract, column 1, examples and claims)."

In response, Applicant respectfully submits that the claims of the present invention recite transfersomes that pass as an entity through a permeability barrier containing pores smaller than the size of the transfersomes. The Examiner's attention is respectfully directed to the phrase "as an entity," (see: claim 31, lines 5-6 and claim 46, lines 6-7) which does not mean, e.g., that each and every transfersome passes through the skin intact. Rather, this phrase is meant to distinguish the transfersomes of the present invention from liposomes and other formulations of the prior art, where drug may in certain circumstances be capable of passing through the skin (e.g., to a small degree) *by itself*, and not by means of its association with a transfersome. In fact, the aforementioned distinction of the meaning of "as an entity," was acknowledged by the Examiner in an interview held on October 22, 1999, between Examiner Kishore, inventor Gregor Cevc and inventor's attorney, Clifford M. Davidson, during the prosecution of parent Application No. 07/844,664 (now U.S. Patent No. 6,165,500).

Additionally, it is noted that claim 31 and its dependent claims specifically call for the ratio of lipid to surfactant to be from about 5.5:1 to 1:500.

In contrast, the EP 0 220 797 reference, at page 2, specifically states that the "amount of the hydrophilic surfactant used is preferably 1 to about 15% by weight based on the weight of the phospholipid used. If it exceeds 15% by weight, the formed liposome may be destroyed." This stated comparison is equivalent to a lipid to surfactant ratio of 100:1 to 6.7:1, which is outside the lipid to surfactant ratio range claimed in claim 31.

Claim 31 in its present form includes the limitation of the ratio of lipid to surfactant outside the range described in EP 0 220 797. This is not surprising, because the liposomes of that reference will not act in accordance with the transfersomes of the present invention. The liposomes exemplified in the examples of this reference include stabilizers, which tend to strengthen the liposomes, or reduce their deformability. In this regard, a Declaration[1] of the inventor, Professor Gregor Cevc, is enclosed herewith which demonstrates that liposomes made in accordance with this reference (e.g., Example 1) are not able to pass through the filter (an Anapore membrane with 20nm pores), whereas transfersomes made in accordance with the invention had a high penetration capability. The surrogate skin model used in the experiments conducted in the Declaration of Prof. Cevc are indicative of whether the transfersomes pass through the skin *as an entity*, and therefore may be used as a test to distinguish transfersome formulations which fall within the present claims from other vesicular formulations which do not (e.g., traditional liposomes).

In view of the above arguments and the evidence presented in the Declaration of Prof. Cevc, it is respectfully submitted that the Examiner's rejection has been overcome and should be withdrawn.

In the Office Action, the Examiner rejected claims 31, 32, 34-42, 46-47, 62-86 and 101-155 under 35 U.S.C. § 102(b) as being anticipated by Mayer. The Examiner stated "Mayer teaches liposomes containing an amphiphilic lipid insulin and a method of preparation (note the abstract and Materials & Methods section)."

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1. This Declaration of Gregor Cevc was originally submitted during the prosecution of parent application Serial No. 07/844,664 (Now U.S. Patent No. 6,165,500).

In response, Applicant respectfully points out that only claims 31-69 are currently pending in the present application. It is believed that the Examiner's rejection of claims 70-86 and 101-155 was the result of the Examiner inadvertently copying into this Office Action text from rejections made during the prosecution of the parent application.

In addition, Applicant respectfully submits that Mayer does not anticipate the claims of the present invention. Mayer does not disclose preparations capable of passing through a permeability barrier, nor does Mayer disclose the claimed preparation wherein the transfersomes have the ratios of lipids to surfactants set forth in the claims. Accordingly, it is respectfully requested that the Examiner withdraw this rejection.

Rejections Under 35 U.S.C. § 103

In the Office Action, the Examiner rejected claims 31-69 under 35 U.S.C. § 103(a) as being unpatentable over EP 0 220 797. The Examiner noted that it was unclear whether EP teaches all the instant functional parameters, but that "in the absence of showing the criticality, they are deemed to be parameters manipulatable by an artisan to obtain the best possible results."

In the Office Action, claim 48 was rejected under 35 U.S.C. §103(a) as being unpatentable over EP 0 220 797, further in view of Mayer cited above, the Examiner stating that it would have been obvious to one of ordinary skill in the art to subject the liposomes of EP to extrusion since such a process produces a homogeneous population of liposomes. Claims 51 and 61-62 were rejected under 35 U.S.C. §103(a) as being unpatentable over EP 0 220 797 and Mayer, individually or in combination further in view of Patel (FEBS Letters), the Examiner stating that encapsulation of active agents such as insulin not taught by EP or Mayer would have been obvious to one of ordinary skill in the art since Patel shows the routine use of liposomes for the encapsulation of insulin and an artisan would expect at least similar results. The Examiner rejected claims 43-45 under 35 U.S.C. §103(a) as being unpatentable over EP 0 220 797 and Mayer cited above, individually or in combination further in view of Wallach (U.S. Patent No.

4,911,928), the Examiner stating that encapsulation of claimed active agents which are not taught by EP or Mayer, would have been obvious to one of ordinary skill in the art since Wallach shows the routine use of liposomes for the encapsulation of these agents and an artisan would expect at least similar results.

Applicant respectfully submits that the present claims are not obvious in view of any of the combinations of prior art set forth above. Independent claims 31 and 46 recite that the transfersomes are able to pass through a permeability barrier containing pores smaller than the size of the transfersomes. Independent claim 31 also specifically calls for the ratio of lipid to surfactant to be from about 5.5:1 to about 1:500. Mayer does not hint or suggest the inclusion of a surfactant, and therefore cannot overcome the deficiencies of EP 0 220 797.

In addition, Patel does not overcome the deficiencies of EP 0 220 797 and Mayer, because Patel does not hint or suggest the inclusion of a surfactant as claimed, and does not hint or suggest that its formulations can pass through a permeation barrier such as skin. Rather, the formulations described in Patel are injected intraperitoneally or administered orally.

Accordingly, it is respectfully submitted that the rejections based on the combination of EP 0 220 797 with either Mayer, Patel, or both references, has been overcome and should be withdrawn.

Wallach describes paucilamellar vesicles which also cannot pass through a permeability barrier or through skin to any significant degree. Wallach does not hint or suggest the claimed ratios of lipid to surfactant. Wallach, in fact, intends for its paucilamellar vesicles to not be substantially deformable because Wallach preferably includes a stabilizer such as cholesterol.

In order to further highlight important differences between the presently claimed invention and the paucilamellar vesicles described in Wallach, the Declaration of the inventor, Professor Gregor Cevc, that is enclosed herewith, demonstrates that liposomes made in accordance with this reference (e.g., Example 1) are not able to pass through the filter (an Anopore membrane with 20 nm pores), whereas transfersomes made in accordance with the invention had a high penetration capability.

In view of the specific limitations to the claims, the arguments presented, and the experimental evidence submitted by the inventor, it is respectfully submitted that the Examiner's rejections based on the combination of EP 0 220 797, Mayer and Wallach has been overcome and should be withdrawn.

Conclusion

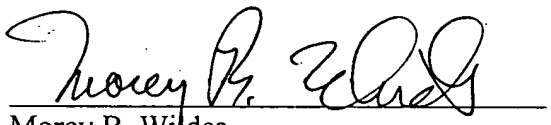
It is respectfully submitted that the issues raised by the Examiner in the Office Action dated December 4, 2000 have been addressed by virtue of this amendment, or via the Declaration of the Inventor submitted herewith, and that this application is now in condition for allowance. If any further issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Accompanying this amendment are (a) the Declaration of the Inventor, Prof. Gregor Cevc; (b) a request for extension of time and (c) Appendix A (marked up amended claims). It is not believed that any further fees are due at this time. If it is determined that additional fees are due, the Commissioner is hereby authorized to deduct said fees from Deposit Account No. 50-0552.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC



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Appendix A- marked-up amended claims

31. (Amended) A preparation suitable for transporting active agents through [though] permeability barriers, comprising a plurality of transfersomes in a medium, said transfersomes comprising a pharmaceutically acceptable surfactant which is compatible with said lipid, the ratio of said lipid to said surfactant enabling said transfersomes to undergo sufficient deformation to enable said transfersomes to pass as an entity through a permeability barrier which has pores smaller than the size of said transfersomes, wherein the total concentration of said lipid in said medium is from about 0.1% to about 30%, by weight and the ratio of lipid to surfactant is from about 5.5:1 to about 1:500.

34. (Amended) Preparation as claimed in claim 31, wherein the concentration of said surfactant is between 20 and 50 mol-% of the concentration of said surfactant which would be required for causing [causes] said lipid to be solubilized, and the edge tension of said transfersomes is about 10 Piconewton or less.

48. (Amended) Method as claimed in claim 46, further comprising determining the stability and the permeation capacity of said transfersomes [the droplets] by means of gravity or pressure filtration, through a fine pore filter.

50. (Amended) Method as claimed in claim 46 wherein the content of said surface active substance is between 20 and 50 mol-% of the concentration of such substance which would be required for causing [that causes] said lipid to be solubilized.